NOTE *Pathology*

Primary Cardiac Fibrosarcoma in a Dog

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ABSTRACT. A primary cardiac fibrosarcoma in the right atrium of a 6-year-old Chihuahua dog is described. At necropsy, there was a firm, whitish and spherical mass in the right atrium. Histopathologically, the mass had moderate cellularity composed of spindle-shaped cells with scattered multinucleated giant cells. The tumor cells were arranged in interwoven bundles and sheets in the collagenous stroma. No metastases were observed. Ultrastructurally, the tumor cells mainly consisted of fibroblasts. Multinucleated giant cells did not have any certain organelles that would indicate a higher order of differentiation. Primary cardiac sarcomas in dogs are extremely rare.
KEY WORDS: canine, fibrosarcoma, heart.

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In dogs, as in man, cardiac tumors show a minimal prevalence [2, 7, 9, 11, 16]. Both primary and metastatic heart tumors may occur in the heart, but primary neoplasms of the canine heart are much less common than metastatic ones [8, 12]. Primary cardiac sarcomas in dogs are extremely rare, and reported cases include fibrosarcoma [1, 15], rhabdomyosarcoma [8], chondrosarcoma [4], osteosarcoma [13], malignant mixed mesenchymal tumor [10] and undifferentiated sarcoma [14]. The present report describes the immunohistochemical and ultrastructural features of the primary cardiac fibrosarcoma in a dog in detail.

A 6-year-old intact male Chihuahua was admitted to the veterinary teaching hospital of Azabu University, suffering from slight weight loss and anorexia of 10 days duration. Prior to presentation at the hospital, removal of pleural effusion and treatment with diuretics had been performed. Physical examination revealed dyspnea without cyanosis. Hematological and biochemical findings showed hyponatremia, hypochrolemia, and neutrophilia. Auscultation revealed no apparent cardiac murmur because heart sounds were too weak. Low voltage without arrhythmia was also noticed on the electrocardiogram. Pleural effusion, obstructing the view of the cardiac silhouette, was visible on radiographs of the chest. After the removal of pleural fluid (approximately 200 m*l*), Levine III/IV systolic regurgitant murmur was clearly heard at the left apex of the heart and furthermore, a radiograph revealed that the cardiac silhouette was visible and the heart appeared to be of normal size. Ultrasonographic examination of the heart revealed pleural effusion, atrial dilatation with the shift to the left side of atrial septum, an increase in the pressure of the right atrium and the mass in the right atrium and the right aterioventricular orifice. Doppler ultrasonography suggested an intracardiac mass interfering with the right ventricular inflow. The clinical diagnosis was tricuspid stenosis due to an intracardiac mass. The dog's general condition became to be deteriorated during the hospitalization period of one week. Pleural fluid accumulated again, despite the removal of pleural effusion and treatment with diuretics, and frequent convulsive seizures of unknown causes also appeared. Euthanasia was done at the request of the owner due to the deteriorated condition and poor prognosis.

The necropsy was performed, and the heart, lungs, liver, spleen, kidneys, duodenum and brain were fixed in 10% neutral buffered formalin and submitted to the pathology department of the veterinary teaching hospital. Formalin-fixed tissue was embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin-eosin (HE), Azan and Watanabe's silver impregnation. Immunohistochemical studies were performed on formalin-fixed paraffin embedded tissues. For immunohistochemistry, anti-vimentin (1:50, monoclonal, Nichirei, Japan), anti-bovine S-100A protein (prediluted, polyclonal, Dako, U.S.A.), anti-neuron-specific enolase (NSE) (prediluted, monoclonal, Dako, U.S.A.), anti-human lysozyme/muramidase (prediluted, Nichirei, Japan), anti-human α1-antichymotrypsin (prediluted, Nichirei, Japan), anti-desmin (1:20, monoclonal, Nichirei, Japan), anti-human alpha-smooth muscle actin (prediluted, monoclonal, Nichirei, Japan) and anti-dog myoglobin (1:2,000, polyclonal, Bethyl Laboratories, U.S.A.) were used. Formalin-fixed tumor tissue was also prepared for electron microscopy following the process as follows; fixed for 24 hr in 2.5% glutaraldehyde solution and then postfixed in 1% osmium teroxide, dehydrated with ascending alcohol, displaced with QY-1 and embedded in epoxy resin. Ultrathin sections of selected areas were double stained with uranyl acetate and lead citrate and examined in a transmission electron microscope (model: JEOL 1210).

At necropsy, there were a small amount of reddish fluid within pleural cavities and a moderately dilated atrial auricle. A firm, whitish and spherical mass, measuring approximately 0.5 cm in diameter, covered with some blood clots was found in the right atrial surface of the atrial septum (Fig. 1). It also extended into the cavity of the right atrial appendage and involved part of the septal leaflet of the tricuspid valve (Fig. 2). The right atrium and atrial auricle were mod-

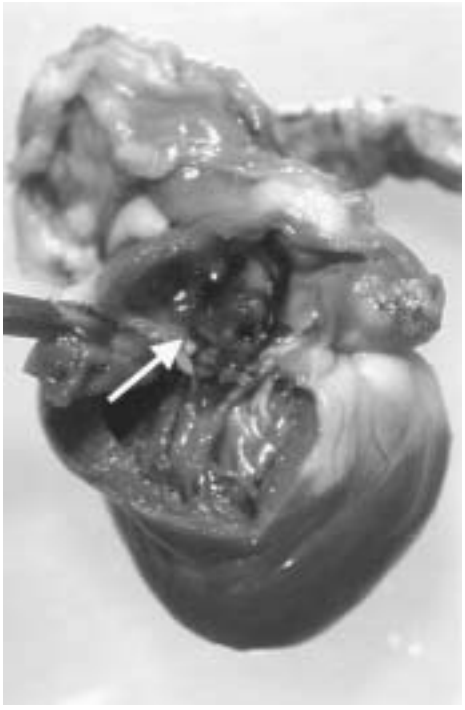

Fig. 1. Gross appearance of the cardiac tumor. Open right heart with fibrosarcoma. A mass in the right atrium. It protruded from the endocardial surface of septal wall of the right atrium (arrow).

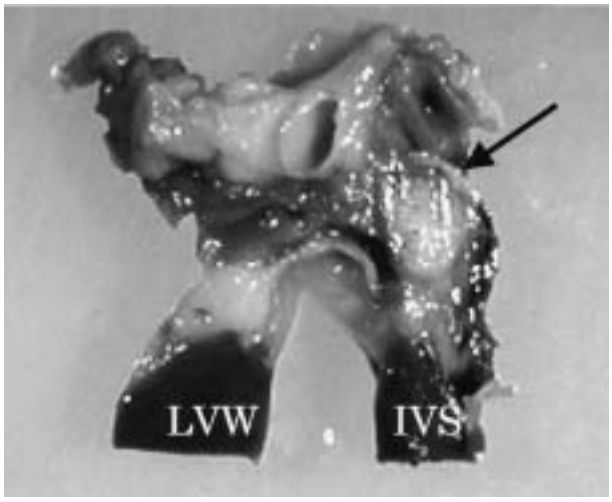

Fig. 2. Paramedian saggital section of the heart. The long axis plane including the interventricular septum and left ventricular wall. A spherical mass (approximately 0.5 cm diameter) (arrow) attached to the base of the septal leaflet of the tricuspid valve. LVW, left ventricular wall; IVS, interventricular septum.

erately dilated owing to the tricuspid orifice stenosis and the tumor mass.

The mass had moderate cellularity composed of moderately pleomorphic, fibrous, oval to plump spindle-shaped

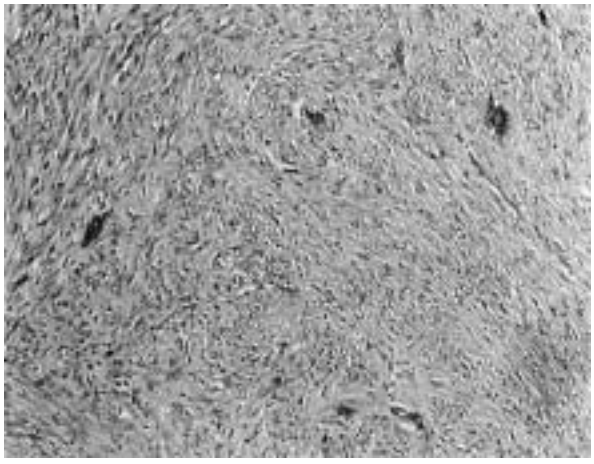

Fig. 3. The mass had moderate cellularity composed of mildly pleomorphic spindle-shaped cells, often arranged in interwoven bundles and sheets in the collagenous stroma. Multinucleated giant cells also scattered. HE, × 300.

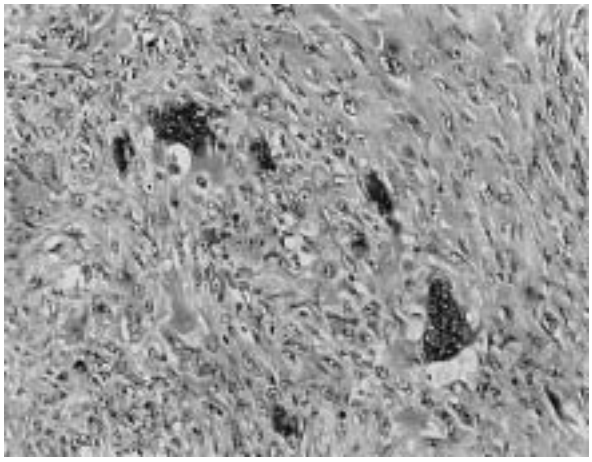

Fig. 4. Multinucleated giant cells associated with a pile of nuclei were scattered throughout the mass. HE, × 600.

cells, often arranged in interwoven bundles and sheets (Fig. 3). The tumor cells contained pale basophilic cytoplasm and finely granular to vesicular fusiform nuclei with a single to a few prominent nucleoli. Multinucleated giant cells associated with a pile of nuclei also scattered throughout the mass (Fig. 4). These multinucleated cells had a variable number of nuclei, ranging from as few as 3–4 to as many as 20–30. There were 0 to 2 mitotic figures/400X high-power fields. The tumor cells were supported mainly by various amounts of collagenous stroma blended with hypocellular areas (Fig. 5). There were also some pale small metaplastic areas with chondroid matrix, especially in the tricuspid valve. The edge of the mass was relatively smooth and the invasion of tumor cells into the myocardium, replacement or compressed atrophy of heart muscles was not observed in the surrounding myocardium. Immunohistochemically, most tumor cells expressed vimentin and some cells also stained

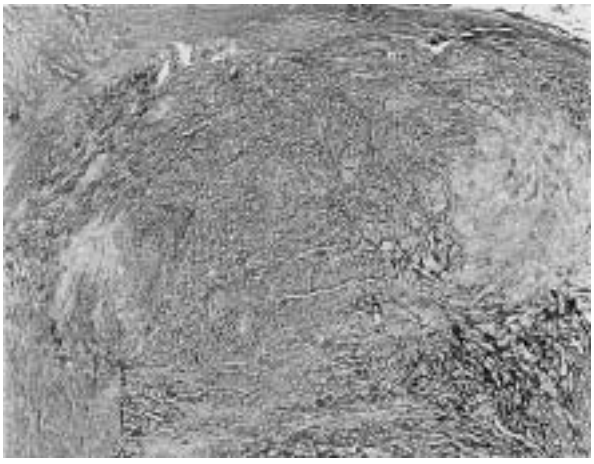

Fig. 5. The tumor cells were supported by collagenous stroma. Azan stain, × 120.

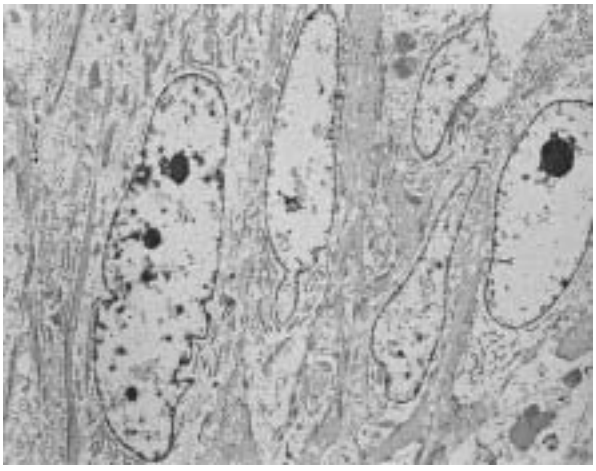

Fig. 6. The spindle-shaped cells. The nuclei were elongated with prominent nucleoli. The cytoplasm includes prominent dilated rough endoplasmic reticulum and a few mitochondria, × 3,000.

for S-100 protein. Most neoplastic cells, except for only a few scattered cells, were negative for desmin, alpha-smooth muscle actin, anti-lysozyme/muramidase and anti-α1-anti-chymotrypsin. All neoplastic cells were negative for myoglobin and NSE.

Ultrastructurally, the tumor cells mainly consisted of fibroblasts (Fig. 6). Nuclei were elongated with prominent nucleoli. Cytoplasmic organelles were sparse, but there were prominent, dilated rough endoplasmic reticulum and a few mitochondria. Some cells also had sparse longitudinally oriented intracellular tracts of thin filaments with focal densities and resembled myofibroblasts. Extracellularly, collagen fibrils were present. Multinucleated giant cells had deeply indented nuclei with irregular nuclear contour scattering throughout the cell. The cytoplasm had scattered rough endoplasmic reticulum and mitochondria, but they did not have any certain organelles that would indicate a higher order of differentiation (Fig. 7). Some giant cells had pyknotic nuclei and extensive alterations in the plasma membranes: marked swelling of mitochondria and accumulation of lipids in the cytoplasm.

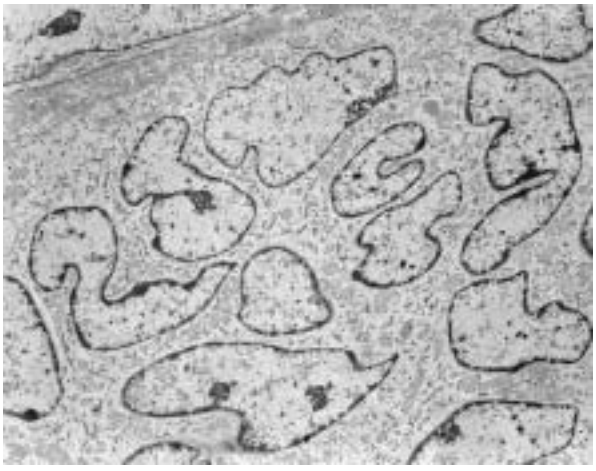

Fig. 7. Multinucleated giant cells. The deeply indented nuclei with irregular nuclear contour scattering throughout the cell. The cytoplasm had scattered rough endoplasmic reticulum and mitochondria, × 3,000.

In addition to the cardiac tumor, sections of the liver, spleen, lungs, jejunum, kidneys, and brain were examined microscopically. Other histopathological findings were limited to the liver, spleen, lungs, and mesentery. In the liver, there was dilatation of hepatic veins and lymphatics with occasional thrombosis, mild to moderate hepatic fibrosis, cholestasis and multifocal vacuolar degeneration of the hepatocytes. Changes in the spleen included mild hemosiderosis and extramedullary hematopoiesis. One section of the left lung lobe showed pulmonary thrombosis. There were small multifocal fat necroses in the mesenteric adipose tissue. No metastases were observed.

In dogs, both primary and secondary cardiac tumors are rare [7, 9] and the primary ones are much less common than the other [8, 12]. Reviews of large autopsy series, including one of 10,090 cases, show the cardiac tumors at a frequency ranging from 0.12–5.73% [16]. The most common primary and/or secondary cardiac tumor is hemangiosarcoma [7], which constituted a total of 60.52% of all heart tumors [16]. Except hemangiosarcoma, the reported cases of the primary cardiac sarcomas in dogs are few [1, 4, 8, 10, 13–15].

The present case was diagnosed as primary cardiac fibrosarcoma, due to the histological and ultrastructural characteristics of the tumor and the absence of neoplastic involvement in the remaining viscera and brain. The diagnosis of fibrosarcoma was based on pleomorphism of tumor cells and mitotic activities. However, in common with the two previously reported canine fibrosarcoma cases [1, 15], no metastases were observed in the present case.

The present cardiac fibrosarcoma was located in the right atrium. In the previous two cases, one filled the right atrium

and protruded into the right ventricle [1], and the other involved the right ventricular free wall, the interatrial and proximal interventricular septa and the right atrial lumen [15]. In dogs, most primary cardiac tumors, either benign or malignant, arise from the right atrium [7], while in human pathology, the preponderant site for the cardiac connective tissue sarcomas is the left atrium [2].

Fibrosarcoma should be differentiated from rhabdomyosarcoma, peripheral nerve sheath tumors (PNSTs), leiomyosarcoma and malignant fibrous histiocytoma (MFH) [3]. In the present case, ultrastructural, histochemical and immunohistochemical studies were useful to rule out rhabdomyosarcoma, PNSTs and leiomyosarcoma, but were of less value in the differential diagnosis between fibrosarcoma and MFH. Several early works have suggested that immunohistochemical evidence of the expression of two histiocytic enzymes, lysozyme/muramidase and α1-antichymotrypsin, may empirically useful for differential diagnosis of MFH, but not completely distinctive [17].

Based on the definitions and explanatory notes widely adapted to the mesenchymal and soft tissue tumors of domestic animals [3, 5], our present case may have borderline features between fibrosarcoma and MFH. On the other hand, according to recent trends in human classification of the soft tissue tumors, collagen-forming tumors diagnosed as fibrosarcoma are located at the low-grade end of a spectrum that places MFH at the high-grade end [17]. Moreover, in a sharper distinction between fibrosarcoma and MFH, fibrosarcoma definitionally cannot contain pleomorphic cells and round histiocyte-like cells including giant cells [6].

In domestic animals, fibrosarcomas, arising from fibroblasts, have variable presentations and more anaplastic tumors can have marked pleomorphism with multinucleated giant cells [3]. While, MFH of domestic animals, although still controversial, arises from a pluripotential mesenchymal cell that shows a fibroblastic/myofibroblastic phenotype [3, 5]. Fibrosarcoma with giant cells exists as a diagnostic entity in domestic animals, but fibrosarcoma with giant cells could be confused with the giant cell variant of MFH; morphological differences between the two are subtle [5].

Predominant cell type is an important additional diagnostic criterion for the differential diagnosis between fibrosarcoma with giant cells and the giant cell variant of MFH in domestic animals; the giant cell component is the minority cell population in fibrosarcoma [3]. Based primarily on the major component of the tumor, the present cardiac tumor was diagnosed to be fibrosarcoma rather than MFH.

The exact cell origin of the present tumor is still unclear, although immunohistochemical and ultrastructural findings suggest that the tumor cells are possibly related to fibroblasts with some differentiation for myofibroblasts. In human pathology, many cardiac sarcomas show a mixture of differentiation patterns, and sarcoma with single differentiation patterns are most unusual. They are usually regarded as arising from undifferentiated mesenchymal cells in the endocardium [2].

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